Embryology and physiology

All 4 major chromosomal abnormalities a/w urogenital abnormality:

Chromosome defect or syndrome	Frequency (%)	Genitourinary anomalies
Turner's syndrome 45X0	60–80	Horseshoe kidney Duplication
Trisomy 18 (Edwards' syndrome)	70	Horseshoe kidney Renal ectopia Duplication Hydronephrosis
Trisomy 13 (Patau syndrome)	60–80	Cystic kidney Hydronephrosis Horseshoe kidney Ureteric duplication
4p (Wolf–Hirschorn syndrome)	33	Hypospadias Cystic kidney Hydronephrosis
Trisomy 21 (Down's syndrome)	3–7	Renal agenesis Horseshoe kidney

<u>Upper urinary tract</u>

From intermediate mesoderm
Arises at 4th week of gestation
3 sequential stages;

- pronephros — segmented, vestigial, recedes
- mesonephros — unsegmented, briefly functional, develops into gonads, drains via mesonephric duct
- metanephros — arises in 5th week (28 days on); Bowman's capsule to DCT arise from metanephric blastema, collecting ducts to ureter from ureteric bud. Interaction of ureteric bud with blastema stimulates productions of nephrons – **reciprocal induction** (Mackie and Stevens) ascent up abdominal wall completed by 10th week, appearance of urine (and bladder) week 10-12; continued production of nephrons until wk 36 (ante or post-natal)

Genes involved in renal development

- WT-1 — Formation of ureteric bud
- Pax-2 — Crucial control gene; Formation of Wolffian & Mullerian ducts, ureteric bud and metanephric mesenchyme
- GDNF — Expressed in metanephric mesenchyme; Ligand for RET receptor on ureteric bud – important for bud/mesenchyme interaction

Renal agenesis

Intrinsic defect of embryonic mesenchyme; Failed induction of nephrogenesis; or involution of multicystic dysplastic kidney
Bilateral renal agenesis fatal, but as placenta does job in utero, may survive till term. Lack of urine = 90% reduction in liquor –

leads to pulmonary hypoplasia and molding abnormalities (hypognathism etc.)
Risk of second child with bilateral renal agenesis ~ 3.5%
Unilateral renal agenesis 1:1500 live births

Renal dysplasia
Defective interaction of ureteric bud with blastema

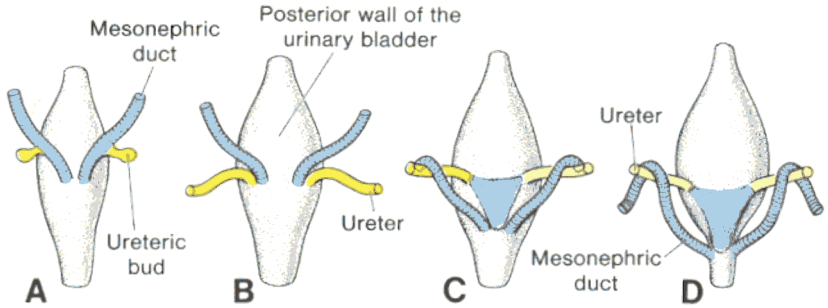
Abnormalities of ascent

Horseshoe	1:400 live births
Pelvic kidney	1:100 – 1:500
X-fused ectopia	1:1000 – 1:2000

Ureter initially solid. Recanalisation mediated by angiotensin/AT2 receptor

Lower urinary tract

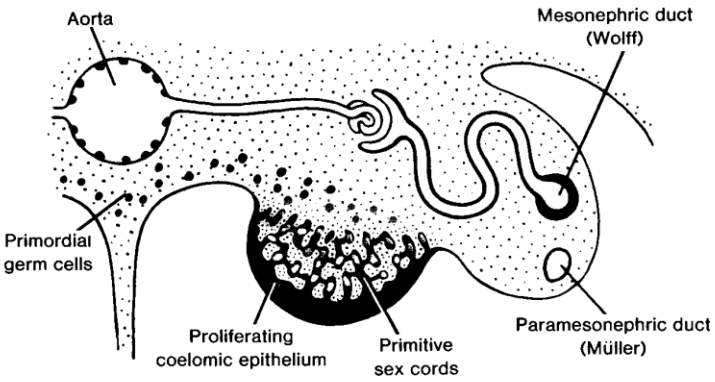
Urorectal septum divides cloaca into anorectal canal and urogenital sinus at 4 – 7 weeks
Ingrowth of Rathke folds divides cloacal membrane into urogenital membrane and anorectal membrane
Allantois vestigial tube formed by folding of fetus. Obliterated to form urachus (median umbilical ligament). Defective closure leads to either fistula, sinus or cyst,
Definitive urogenital sinus (at level of urogenital membrane) enlogates to form penile urethra in male
Cranial ascent of ureters and growth of bladder (endoderm) lead to formation of trigone (mesoderm) and separation of mesonephric ducts from ureteric buds (see view from behind, below)



Mesonephric ducts become ejaculatory ducts in this area
Prostate develops at end of third month from prostate urethra buds penetrating into surrounding mesenchyme. Formation complete at 15th week

Genital system

Gonadal ridges form medial to mesonephos from week 3
Migration of primordial germ cells from yolk sac week 6 to form primitive sex cords in indifferent gonads: at same time paramesonephric duct develops adjacent to MD



Male genitalia

Presence of testis-determining gene (SRY) on Y-chromosome stimulates male differentiation at around week 7

Testis determining factor (product of SRY) causes:

- Medullary sex cord development into Sertoli cells*
- Regression of cortical cords
- Tunical albuginea development

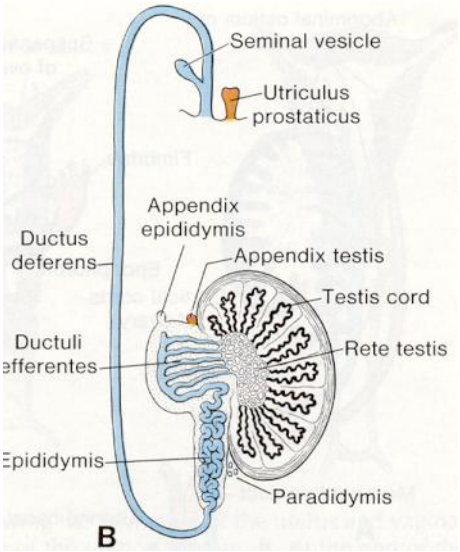
* Sertoli cells produce Mullerian inhibitory substance (MIS), causing:

(i) Regression of paramesonephric ducts (vestiges = appendix testis and prostatic utricle)

(ii) Production of testosterone by Leydig cells (week 9). Leydig cells formed from mesenchyme of genital ridge

(iii) First stage of testicular descent

Mesonephric (Wolffian) duct gives rise to: rete testis, ductuli efferentes, epididymis, appendix epididymis, ductus deferens (vas), seminal vesicle and ejaculatory ducts. Development of MD under T control.



Testis descent in 2 phases:

1. MIS stimulated along gubernaculum to inguinal ligament (wks 8-25)
2. T stimulated along gubernaculum to scrotum (wks 25-30)

Vaginal protrusion of peritoneum also follows gubernaculums, taking with it layers of abdominal wall to for inguinal ligament. Processus vaginalis obliterated at birth or shortly after (patent processus vaginalis lead to congenital hydrocoele – abnormal patency if still present at one year)

External genitalia
- Under influence of dihydrotestosterone
- Genital tubercle elongated to form phallus
- Lateral growth and infolding forms penile urethra (endoderm)
- Small ectodermal ingrowth from glans to form navicular fossa
- Complete at 15 weeks

Testosterone
- Half-life in serum 10-20 mins
- Circulating testosterone in 3 forms:

2%	free	bioavailable
38%	albumin-bound	bioavailable
60%	SHBG	not bioavailable

- Metabolised by glucoronidation by liver – excretion by kidney

<u>Female genitalia</u>

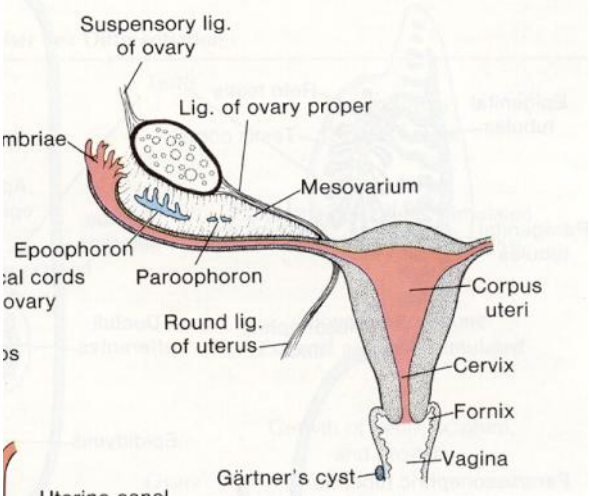
Default sex differentiation is female

In the absence of SRY gene indeterminate gonad develops into ovary: cortical cords develop, medullary cords degenerate and no tunica albuginea.

Primordial germ cells embark upon first meiotic division then arrest till puberty

Cranial genital ligament forms suspensory ligament of ovary. Caudal portion (rudimentary gubernaculum) forms ligament proper and round ligament (ending in labial fold)

Without SRY mullerian duct regresses (vestiges = epioophoron, paraoophoron +/- Gartner's cysts)



Descent of ovary and intracoelomic growth of genital ridges results in upper portion of paramesonephric deviating laterally, whilst lower portion fuses in the midline to form uterus and cervix and upper two-thirds of vagina. Fusion results in formation of broad ligament on each side. Sinovaginal bulb develops at urogenital sinus to form lower third vagina. Hymen separates vagina from urogenital sinus.

<u>Abnormalities</u>

Kleinfelter's	47 XXY; phenotypically male nondysjunction during spermatogenesis (40%) or oogenesis (60%); 1:500 males;

	infertility, gynaecomastia, underandrogenisation
Turner's	45 X; phenotypically female streak ovaries, infertility, no puberty (no E)
Pure gonadal dysgenesis	46XX; phenotypically female. Failure of migration or development of germ cells. Normal chromosome complement but absent ovary, pre-pubertal sex characteristics and infertile
Testicular feminization	aka androgen insensitivity syndrome 46 XY but phenotypically female testis and MIS therefore no ovary/uterus and blind-ending vagina. UDT common
Androgenital syndrome	aka congenital adrenal hyperplasia 46 XX; phenotypically male 21-OH hydroxylase deficiency = androgens with virilisation of external genitalia (clitoral enlargement and partial fusion of labia)
Rokitansky syndrome	agenesis of upper two thirds of vagina – failure of fusion of paramesonephric ducts. Other fusion abnormalities include uterus didelphs (+/- double vagina), bicornate uterus etc.

Paediatric renal physiology

Fetal urine production commences at 10-12 weeks gestation.
Urine production reaches 30ml/hour at 32 weeks onwards
Nephron production ceases at 36 wks
Mean number of nephrons at term ~ 700,000 to 1 million
At birth:

- All children void within 24 hours, irrespective of gestational age
- Impaired concentrating ability
- Impaired sodium handling
- Impaired acid-base regulation (Mild mixed acidosis typical in neonates, due to impaired bicarbonate reabsorption)
- Low renal blood flow
- GFR 12ml/min/m^2 (doubles by 2 weeks; 'normal' by 2 yrs).
- Improvement in GFR multifactorial:
  - Diminished renal vascular resistance
  - Increasing perfusion pressure
  - Improved glomerular permeability
  - Increased filtration surface
- Elevated serum creatinine reflects maternal levels. Decrease by ~50% in first week of life.
- Compensatory hypertrophy in unilateral renal agenesis occurs in utero

Renal impairment in children

CRF in children leads to growth retardation, sexual immaturity and psychomotor or intellectual retardation
CRF defined as GFR 25-30% normal
Main causes in children

- Glomerulonephritis (focal segmental glomerulosclerosis)*
- Congenital (hypoplastic/dysplastic/reflux)
- Collagen vascular disease
- Obstructive nephropathy

* diseases a/w immune complex deposition (SLE, post-infectious membranoproliferative, not IgA nephropathy) result in low circulating complement levels

Serum creatinine at 6 months reliable indicator of outcome

Serum creatinine μmol/l at 6 months of age	Prognosis (predicted age of onset of end-stage renal disease)
<150	Good
150–300	ESRD 10+ years
200–350	ESRD 5–10 years
350–600	ESRD <5 years
>600	Uncertain outcome

Visible haematuria and respiratory tract infections

After URTI	Post-infectious (streptococcus etc.)
Concomitant	IgA nephropathy
	Alport's hereditary nephritis

Consequences of renal failure in kids

Malnutrition	anorexia, N+V
Renal osteodystrophy	rickets* in young
	Slipped epiphysis, long bone abnormalities in older kids**
Anaemia	impaired epo production

* rickets = rachitic rosary (prominent costochondral joints), metaphysical widening, frontal bossing, craniotabes (abnormal softening of skull bones)
** often varus/valgus deformities. X-ray features = subperiosteal resorption, ground-glass mottling, focal lucency or sclerosis. Also heterotopic calcification

Table 33.1.
Estimated Urethral Catheter Size

Age	Catheter Size
Newborn	5 French (feeding tube)
3 mos	8 French
1 yr	8–10 French
3 yr	10 French
6 yr	10 French
8 yr	10–12 French
10 yr	12 French
12 yr	12–14 French
Teen/adult	16+ French

Table 33.2.
Formula for Predicting Bladder Capacity

Age	Bladder Capacity
<1 yr	wt (kg) × 10 = mL
>1 yr	(age + 2) × 30 = mL*

* Maximum volume = 400 mL

<u>Resuscitation in children</u>

20ml/kg fluid bolus
4ml/kg/hr maintenance infusion

<u>Antibiotic treatment in kids</u>

4ml/kg gentamicin IV
4mg/kg timethoprim PO
2mg/kg trimethorprim PO prophylaxis

<u>Bladder compliance</u>
3 components:
(i) Bladder unfolding
(ii) Elasticity
(iii) Viscoelasticity

Elasticity *Property of a body or substance that enables it to resume its original shape after a distorting force is removed*
Viscosity *Resistance of a subject to flow – related to the concept of shearing force. Usually different layers of a fluid exerting a shearing force on each other*

Paediatric radiology

USS Expected bladder capacity
- < 1 year: Weight in kg x10
  Alternatively Holmdahl formula (ml)
  38 + (age in mo. X 2.5)
- > 1 year: Koff formula (ml)
  (age+2) x 30

Significant residual volume if >10% expected capacity
Bladder wall thickening highly suggestive of BOO
AP diameter > 10mm suspicious for PUJO or reflux
Liver usually brighter than kidney, except in first 3 months, with infection or end-stage kidney

MCUG Requires catheterization for filling, followed by removal and voiding
NICE recommends 3 days oral antibiotic cover for MCUG
Gold-standard for reflux; only way of imaging urethra, but high radiation, distressing and UTI
Steep oblique/lateral views to exclude valves in boys
Entire penile urethra needed to exclude anterior lesions (rare)
May be substituted for indirect MAG-3 cystography, which a/w low radiation and not as distressing, but low sensitivity for lower grades of reflux and requires co-operative kids. Best reserved for follow-up

DMSA 99-technetium labeled **dimercaptosuccinic acid**
Scintigraphy or renography
Gold-standard for scarring – typically polar areas of decreased uptake; also good for ectopic kidneys
Initial injection followed by scan at 3-4 hours
Relative uptake should be equal within 10% tolerance
False positives in acute infection – transient 'nephronia': allow 8 weeks after infection for DMSA to be accurate

MAG-3 99 metastable technetium labeled **dimercaptoacetyltriglycine**
99-technetium manufactured in a cyclotron
90% MAG-3 filtered, 10% secreted cf. filtration only with DTPA (diethylenetriaminepentamic acid) - therefore good signal to background ration and easy to interpret curves.
Better for patients with renal impairment but still unreliable if GFR < 15ml/min
Dynamic renography

0-10 secs	Vascular phase
10secs – 5mins	Uptake phase (used to calculate split function)
5 mins onwards	Excretory phase

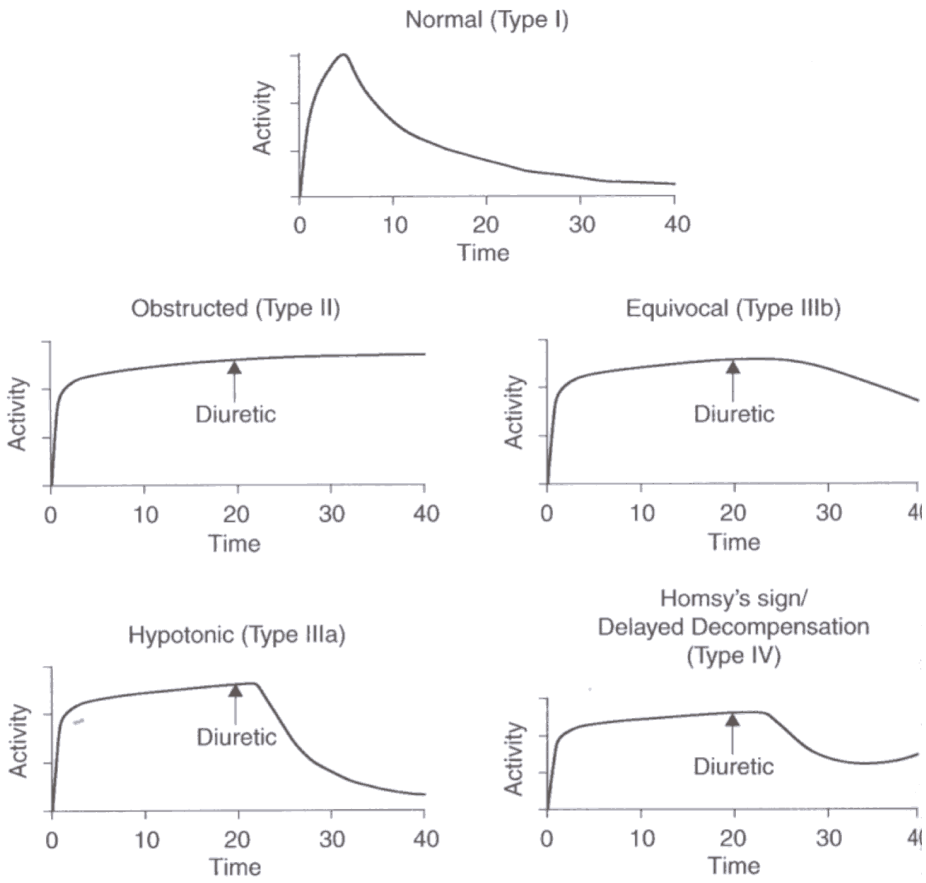
Diuretic administration
- Maximum effect of frusemide after 18 mins
- Therefore maximum effect at 38 mins on standard F+20
- Equivocal rate of 15% for F+20; most accurate F-15 (reduces equivocal rate to ~7%) but difficult to perform

F+0 happy medium - recommended

Interpretation

I	Normal
II	Obstructed
IIIa	Hypotonic (Baggy)
IIIb	Equivocal
IV	Delayed decompensation (Homsey's curve) – obstruction with increased urinary flow

NB. F-15 renogram recommended for Type IIIb and IV curves



CT Excellent for renal lesions (trauma and tumour). Better for pulmonary mets than MRI

MRI Better for pelvic tumours, bony metastases and intraspinal extension
Gadolinium for vascular tumours

*99-Technetium extracted from molybdenum 99 generator; half-life 6 hours

Appendix